

### Remarks

The Office Action mailed May 7, 2002, has been received and reviewed. Claims 2, 4, 11, 14, 15, 19-22, 24 and 25 were identified as pending. Claim 20 was withdrawn from further consideration as assertedly drawn to a nonelected invention. The withdrawal of the claim objections and the withdrawal of the rejection under 35 U.S.C. § 112, ¶2 of claims 2, 4, 11, 14, 15, 15, 19, 21, 22, 24 and 25 is noted with appreciation. Applicants propose to amend claims 2, 4, 11, 21, and 22. Entry of the proposed amendments and reconsideration of the application is respectfully requested. A petition to revive and a request for continued examination are filed concurrently herewith.

### Objection to the Specification

The amendment to the specification was objected to as assertedly introducing new matter into the application. The Office Action states: "The added material that is not supported by the original disclosure is the phrase 'or other diagnostic marker known in the field.'" Applicants respectfully traverse this objection. At the fifth paragraph on page 16 of the as-filed application, the specification states:

"Specific detection of said antibodies in the serum can be achieved by labelled peptides. The label can be any diagnostic marker known in the field of *in vitro* diagnosis, but most preferred (and widely recognized) are enzymes, dyes, metals and radionuclides, such as <sup>67</sup>Ga, <sup>99m</sup>Tc, <sup>111</sup>In, <sup>113</sup>In, <sup>123</sup>I, <sup>125</sup>I or <sup>131</sup>I."

Applicants thus respectfully submit this language is supported by the application as-filed, and request the objection to the specification be withdrawn.

### Objection to the Claims

Claims 21, 22, 24 and 25 were objected to as claims 21 and 22 were assertedly drawn in the alternative to the subject matter of a non-elected invention. Claims 21 and 22 have been amended to remove the alternative and applicants respectfully submit no further action is required on this point.

**Claim Rejections under 35 U.S.C. § 112, ¶1**

The rejection of claims 21, 22, 24 and 25 under 35 U.S.C. § 112, ¶1 was maintained from the prior office action. As amended, claims 21 and 22 recite a vaccine that comprises the peptide of either claim 4 or claim 2, respectively. Claims 24 and 25 depend from claims 21 and 22, respectively. The vaccine of claim 21 comprises a peptide of SEQ ID NO:1 capable of inducing an increased binding affinity towards lymphocytes than a peptide that has a threonine at position 2 (SEQ ID NO:9) and the lymphocytes are directed against metastatic melanomas. The vaccine of claim 22 comprises a peptide of SEQ ID NO:9, wherein the threonine at position 2 is substituted with a valine. The peptide is capable of inducing an increased binding affinity towards lymphocytes than a peptide that has a threonine at position 2 and the lymphocytes are directed against metastatic melanomas.

The test for enablement under 35 U.S.C. § 112, ¶1, requires the Office to first determine the breadth of the claims with respect to the disclosure and second, to determine whether one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation. MPEP § 2164.08.

In the Office Action, it is asserted that these claims are not enabled because they are “drawn to a vaccine comprising the peptide of claims 2 or 4, which according to the specification can be used to treat a patient diagnosed with melanoma.” However, the Office Action acknowledges “the specification teaches that the claimed invention can be used to treat patients that have been diagnosed with melanoma....”

In their prior response, applicants pointed out that since the rejected claims specifically recite peptides and vaccines, the prior office action appeared to be objecting to a possible use to which the peptides and vaccines might be put and not to the claimed invention itself. In a rather confusing discussion, the Office Action Made Final cites a particular definition of “vaccine.” The definition is then used as a basis to opine that the claimed invention is not fully enabled. The Office Action thus continues to focus on a potential use of the claimed peptides and vaccines to treat melanomas, and does not take into account what is actually being claimed (the peptides and vaccines). It concludes these claims are lacking enablement “in the absence of working exemplification” (Office Action at page 4).

Applicants respectfully submit that the specification adequately enables one of skill in the art to make and use these vaccines as claimed. The peptides of these vaccines, as claimed, are able to induce an increased binding affinity towards lymphocytes in comparison to a peptide that has a threonine at position 2 and where the lymphocytes are directed against metastatic melanomas. As discussed in the prior response, the peptide recited in claim 2 (that is an element of claim 22), which substitutes a threonine for a valine at position 2, also elicited a greater immune response than SEQ ID NO:9. (See FIGs. 4 and 5). In the Office Action Made Final, this difference in immune response was acknowledged, but was stated “not to appear to be statistically significant.”

In the prior response, applicants discussed the lack of need for a working example under the controlling law and Office rules. The Office Action acknowledges that “Applicants are not required to disclose working exemplification of the claimed invention” (Office Action at page 6), but as discussed previously herein, refuses to acknowledge enablement without such a working example.

As set forth at MPEP § 2164.02, while the “[l]ack of a working example . . . is a factor to be considered . . . [b]ut because only an enabling disclosure is required, applicant need not describe all actual embodiments”. Further, the Federal Circuit has considered this matter and determined that requiring a working example in patents would discriminate against applicants based upon the fact that they are at an early stage in the development of a pharmaceutical product. *Cf. Cross v. Iizuka*, 753 F.2d 1040, 1051, 224 U.S.P.Q. 739,747-48 (Fed. Cir. 1985), *In re Brana*, 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) (“Were we to require Phase II [FDA] testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many areas such as the treatment of cancer”). To require working examples, although not Phase II testing, continues to eliminate the incentive to pursue research in this area, and the Federal Circuit guidance supports a conclusion that no working example is required.

In summary, the rejected claims do not recite treating or preventing melanomas in a patient and, therefore, it is therefore improper to reject these claims based on this limitation. The specification provides an enabling disclosure as to the manufacture and use of the claimed vaccines including an ability to increase binding affinity acknowledged in the Office Action. Applicants thus

respectfully submit that the requirements of 35 U.S.C. § 112, ¶1 are met and that to require a working example of a potential use of the vaccines to support enablement is contrary to both Office rules and the controlling law. Therefore, it is respectfully requested that the rejection of claims 21, 22, 24, and 25 be withdrawn.

Claims 2, 4, 14, 15, 19, 21, 22, 24 and 25 stand rejected under 35 U.S.C. § 112, ¶1 in the Office Action as assertedly containing subject not described in the specification in such a way as to reasonably convey that the inventors had possession of the claimed invention at the time the application was filed. The Office Action asserts that claims 2 and 4 contain new matter with respect to the language “capable of inducing an increased binding affinity towards lymphocytes.” The Office Action requests applicants point to disclosures that provide basis for this element. Applicants note that claims 2 and 4 have been amended to modify this language. Basis for this element may be found at Example 3 at page 25 of the as-filed application, which details the improved binding affinity of peptides to lymphocyte target cells. Accordingly, applicants respectfully submitted that claims 2, 4, 14, 15, 19, 21, 22, 24 and 25, comply with the requirements of 35 U.S.C. § 112, ¶1 and request this rejection withdrawn

**Claim Rejections under 35 U.S.C. § 112, ¶2**

Claims 2, 4, 11, 14, 15, 21, 22, 24 and 25 stand rejected under 35 U.S.C. § 112, ¶2 in the Office Action as assertedly being indefinite. The Office Action states the claims are vague and indefinite with respect to the language: “wherein said peptide is capable of inducing an increased binding affinity towards lymphocytes” in claims 2 4 and 11. The Office Action states the language “capable of” is vague and indefinite as it “cannot be ascertained whether the claims require the peptide to be able to induce an increased binding efficiency”, because “increased is a relative term” and that “the specification does not teach that the peptide can ‘induce’ an increased binding affinity.” Applicants have amended claims 2, 4, 11 and 22 to replace the language “capable of” with the language “is able to”. Applicants further submit that the term “increased” is defined in the claim by reference to the peptide in comparison to which the peptide of such claim is able to induce an increased affinity, and that as discussed previously herein, the specification teaches improved

binding affinity. Accordingly, it is respectfully submitted the amended claims are definite and applicants request they be allowed.

### **Claim Rejections under 35 U.S.C. § 102**

The rejection of claims 2, 11, 22 and 25 under 35 U.S.C. § 102(e) as assertedly being anticipated by U.S. Patent 5,844,075 issued to Kawakami et al. ("Kawakami") was maintained from the prior office action. Applicants respectfully traverse this rejection.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Brothers v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F2d. 1226, 1236 (Fed. Cir. 1989). *See*, MPEP at § 2131.

As discussed in the prior response, Kawakami discloses a peptide, referred to as SEQ ID NO: 46, having the same sequence as that disclosed in SEQ ID NO:9 of the present application (*see* Kawakami at column 24, line 60). The Office Action notes that Kawakami does contain a discussion of possible amino acid substitutions that runs from column 14, line 45 to column 15, line 48 of the Kawakami specification. In this discussion, it is stated that any amino acid may be used to substitute or replace the first, second and last position of the peptide. The listing of exemplary amino acids includes valine. The peptides that may be modified are listed at the end of this discussion at Kawakami column 15, lines 8-12, which state:

Examples of MART-1 peptides that may be modified include, but are not limited to AAGIGILTV (SEQ ID NO: 4), EAAGIGILTV (SEQ ID NO: 17) and AAGIGILTVI (SEQ ID NO: 18) (peptides are presented in single letter amino acid code).

The proposed modification of SEQ ID NO: 46 is thus not disclosed by this language. As discussed in the prior response, the various possible modifications to SEQ ID NO: 46, such as amino acid substitutions, are disclosed in Column 25, lines 1-28 of Kawakami. Kawakami Table 15 discloses the specific, modified peptides that were made. Each modified peptide listed in Table 15 was tested to determine whether its binding affinity to HLA-A2.1 and its recognition by reactive T-cells was

increased or decreased in comparison to SEQ ID NO: 46. None of these modified peptides comprises a valine at position 2 of SEQ ID NO: 46.

In contrast, as amended, claim 2 recites a peptide which comprises at least part of the amino acid sequence of SEQ ID NO:9, wherein the original amino acid at position 2 is substituted with a valine. The peptide of claim 2 is able to induce an increased binding affinity towards lymphocytes and the lymphocytes are directed against metastatic melanomas.

Since none of the peptides listed in Table 15 have a valine at position 2, Kawakami necessarily does not disclose a peptide having the claimed sequence, wherein the peptide is able to induce an increased binding affinity towards lymphocytes and the lymphocytes are directed against metastatic melanomas. Since these limitations are not disclosed, claim 2 is not anticipated by Kawakami.

Claims 11, 22 and 25 distinguish from Kawakami for the same reasons. Accordingly, applicants request this rejection be withdrawn and the claims allowed.

#### **Claim Rejections under 35 U.S.C. § 103**

Claims 2, 11, 14, 19, 22 and 25 stand rejected under 35 U.S.C. § 103(a) as being assertedly unpatentable over Kawakami. The rejection of claims 2, 11, 14, 22 and 25 was maintained from the prior Office Action. The rejection of claim 19 appears to be new. Applicants respectfully traverse these rejections.

As previously discussed, Kawakami does not disclose all the elements of amended claim 2. Since Kawakami does not teach or suggest a peptide, which comprises at least part of the sequence of SEQ ID NO: 9, having a valine at position 2, wherein the peptide is able to induce an increased binding affinity towards lymphocytes and that the lymphocytes are directed against metastatic melanomas, Kawakami does not teach or suggest all of the elements of claim 2. Therefore, claim 2 is not obvious over Kawakami. Claims 14, 19, 22, and 25 are distinguished from Kawakami for depending from claim 2.

Claim 11 recites a method of isolating melanoma antigen reactive tumor infiltrating lymphocytes. The method comprises, among other things, reacting tumor infiltrating lymphocytes with a peptide comprising at least part of the amino acid sequence of SEQ ID NO:9. The peptide

also comprises a valine at position 2 and is able to induce an increased binding affinity towards lymphocytes and the lymphocytes are directed against metastatic melanomas. Since Kawakami does not does not teach or suggest these elements, for the reasons previously discussed, claim 11 is allowable.

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**ENTRY OF AMENDMENTS**

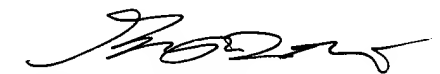
**OFFICE OF PETITIONS**

The proposed amendments to the claims herein should be entered by the Office because the amendments are supported by the as-filed specification and drawings and do not add any new matter to the application. Further, applicants believe the amendments do not raise new issues or require a further search. In the event the Office determines such amendment would raise new issues, applicants note the filing of a request for continued examination herewith, entitling the application to examination on such issues.

**Conclusion**

In view of the remarks and amendments, applicants respectfully submit that the claims, as proposed to be amended, define patentable subject matter. If questions should remain after consideration of the foregoing, the examiner is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



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**MARKED UP VERSION SHOWING CHANGES MADE**

**IN THE CLAIMS:**

Please amend the claims as follows:

2. (Three Times Amended) A peptide comprising at least part of the amino acid sequence of SEQ ID NO:9, wherein said original amino acid at position 2, threonine, is substituted with a valine, wherein said peptide is [capable of inducing] able to induce an increased binding affinity towards lymphocytes than said peptide comprising a threonine at position 2, and wherein said lymphocytes are directed against metastatic melanomas.

4. (Four Times Amended) A peptide comprising the amino acid sequence of SEQ ID NO:1, wherein said peptide is [capable of inducing] able to induce an increased binding affinity towards lymphocytes than a peptide comprising the amino acid sequence of SEQ ID NO:9, and wherein said lymphocytes are directed against metastatic melanomas.

11. (Four Times Amended) A method for isolating melanoma antigen reactive tumor infiltrating lymphocytes, said method comprising the steps of:

- a. taking a sample of a melanoma from a subject;
- b. isolating tumor infiltrating lymphocytes from said sample;
- c. reacting said tumor infiltrating lymphocytes with a peptide comprising at least part of the amino acid sequence of SEQ ID NO:9, wherein an original amino acid at position 2 of SEQ ID NO:9 is substituted with a valine, or an original amino acid at position 8 of SEQ ID NO:9 is substituted with an alanine, and wherein said peptide is [capable of inducing] able to induce an increased binding affinity towards lymphocytes than a peptide not comprising either of said substitutions, to form an antigen-lymphocyte complex;



- d. obtaining tumor infiltrating lymphocytes reacted with said peptide comprising at least part of the amino acid sequence of SEQ ID NO:9 from said reaction mixture of step c.; and
- e. recovering lymphocytes from said antigen-lymphocyte complex thus isolating melanoma antigen reactive tumor infiltrating lymphocytes.

21. (Two Times Amended) A vaccine comprising the peptide of claim 4 [or a nucleotide sequence encoding said peptide], wherein said peptide is [capable of inducing] able to induce an increased binding affinity towards lymphocytes than a peptide comprising the amino acid sequence of SEQ ID NO:9, and wherein said lymphocytes are directed against metastatic melanomas.

22. (Two Times Amended) A vaccine comprising the peptide of claim 2 [or a nucleotide sequence encoding said peptide], wherein said peptide is [capable of inducing] able to induce an increased binding affinity towards lymphocytes than a peptide comprising the amino acid sequence of SEQ ID NO:9, and wherein said lymphocytes are directed against metastatic melanomas.